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Longitudinal changes in pulmonary function and respiratory impedance of rheumatoid arthritis

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ABSTRACT

The aim of this study was to examine long-term changes in pulmonary function and respiratory impedance (Zrs) as assessed by forced oscillation technique (FOT) of rheumatoid arthritis (RA)-related pulmonary disorders. Data of 42 RA patients who underwent pulmonary function tests and Zrs measurements at least twice at a > 900-day interval were retrospectively reviewed. Zrs, respiratory resistance (Rrs) and reactance (Xrs), were measured as a function of oscillatory frequency from 4 to 36 Hz. The Rrs and difference between inspiratory and expiratory phases of Xrs were significantly decreased. Annual changes in Xrs parameters significantly correlated with those of spirometric parameters. Zrs parameters were significantly different between the low (the lower 75 percentile of incidence) and high (the top quartile) frequency of adverse respiratory event groups. The Zrs combined with spirometry may be beneficial to evaluate alterations in respiratory functions of RA.

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with extra-articular diseases including pulmonary diseases. RA-related pulmonary disorders, specifically interstitial pneumonia (IP) and airway abnormalities, are recognized as important extra-articular manifestations because they are responsible for a significant portion of the mortality (Tsuchiya et al., 2011; Nakamura et al., 2012; Assayag et al., 2014). Moreover, risks of complications of respiratory infection and drug-induced lung injury are increased in RA patients treated with disease-modifying antirheumatic drugs (DMARDs) (Tokuda et al., 2017). Importantly, the incidence of respiratory adverse events in RA patients with pre-existing respiratory involvement specifically IP and airway abnormalities is higher than that without respiratory involvement during biological DMARDs therapy (Curtis et al., 2015; Matsumoto et al., 2018). Thus, it is important to carefully manage pulmonary abnormalities by both radiological and physiological assessments of patients with RA (Cortet et al., 1997).

Forced oscillation technique (FOT) is a method to assess respiratory mechanics from input impedance measurements (Dubois et al., 1956; Grimby et al., 1968; Michaelson et al., 1975). Measurement of respiratory system impedance (Zrs), respiratory resistance (Rrs) and reactance (Xrs), has been used to assess respiratory functions in pulmonary diseases, specifically asthma and COPD (Dellaca et al., 2004; Hasegawa et al., 2015; Shirai and Kurosawa, 2016; Ito et al., 2017). It is expected that FOT will be able to identify respiratory abnormalities that are not detectable by spirometric examinations (Oostveen et al., 2013; da Costa et al., 2014; Ito et al., 2017). Moreover, FOT has been used to characterize respiratory mechanics of interstitial lung disease and RA-related pulmonary diseases (Faria et al., 2012; Sugiyama et al., 2013; Fujii et al., 2015; Sokai et al., 2016). Several studies have investigated the longitudinal changes in pulmonary functions of RA (Linstow et al., 1994; Fuld et al., 2003; Zamora-Legoff et al., 2017), but the parameters of the long-term changes in Zrs of RA are not known.

The purpose of this retrospective study was to investigate long-term changes of pulmonary function and Zrs as assessed by spirometry and

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FOT in patients with RA-related pulmonary abnormalities. In addition, relationships between Zrs results and clinical parameters, such as type of pulmonary disease based on chest computed-tomography (CT) findings and complications of respiratory adverse events were evaluated.

2. Methods

2.1. Subjects

The records of patients who met the 1987 American College of Rheumatology classification criteria for RA and attended the outpatient clinic of the Department of Respiratory Medicine, Nagoya University Hospital from April 2010 to August 2016 were retrospectively reviewed. Forty two patients who underwent CT examination and had both Zrs and pulmonary function measured at least twice at a > 900-day interval were enrolled in this study. A flow chart illustrating the inclusion process is shown in supplementary Fig. 1. Pulmonary function was measured in 144 RA cases. Of the 144 cases, both pulmonary function test and Zrs measurement were performed at least twice at a > 900-day interval in 45 cases. Three cases who underwent lung surgery during the interval were excluded. Finally, 42 cases were included in the analysis. This retrospective study was approved by the local ethics committee of Nagoya University Hospital (approval No. 2015-0061). No patient identifiers were included. The informed consent requirement to participate and publish was waived for this retrospective analysis.

2.2. Respiratory impedance measurements

Zrs data were collected by FOT using a commercially available machine (MostGraph-01; Chest M.I., Tokyo) that generates a broadband waveform at frequencies from 4 to 36 Hz in 4-Hz steps as described previously (Uchida et al., 2013; Sokai et al., 2016; Ito et al., 2017). Briefly, impulse oscillatory signals generated by a loudspeaker at intervals of 0.25 s were applied to the respiratory system during tidal breathing at rest. The Zrs was calculated using the system computer algorithms. The Zrs was recorded for approximately 20 s during 5 to 6 respiratory cycles while the patients firmly supported their cheeks with their palms and with their nose clipped in the sitting position with the neck in a comfortable neutral posture. Upper airway artifacts resulting from glottal changes, air leaks, and cheek support techniques during measurements (Peslin et al., 1985; Uchida et al., 2013; Bikov et al., 2015) were carefully eliminated. Three to five technically acceptable measurements were performed as recommended in the guidelines (Oostveen et al., 2003).

2.3. Analysis of impedance results

The actual values of Rrs and Xrs at given frequencies between 4 and 36 Hz were analyzed (Sokai et al., 2016; Ito et al., 2017). FOT enables measurement of both inspiratory and expiratory parameters during tidal breathing (Cauberghs and Van de Woestijne, 1992; Peslin et al., 1992; Dellaca et al., 2004; Sokai et al., 2016). Each Zrs parameter was expressed as a mean value during a respiratory cycle, whole-breath, inspiration, and expiration. The difference between inspiratory and expiratory phases of Rrs ($Rrs_{Insp\text{-}Exp}$) and Xrs ($Xrs_{Insp\text{-}Exp}$) were calculated as mean inspiratory values minus mean expiratory values (Sokai et al., 2016; Ito et al., 2017). Rrs reflects the extent of airflow obstruction (Di Mango et al., 2006; Hasegawa et al., 2015). Under normal conditions, Xrs is determined by the elasticity of the respiratory system at the lowest frequency and the inertial properties at higher frequencies (Oostveen et al., 2003; Goldman et al., 2005). $Xrs_{Insp\text{-}Exp}$ at low frequencies is useful for detecting the expiratory flow limitation in patients with COPD (Dellaca et al., 2004). The values of Rrs were compared with the reference values measured using the same machine (MostGraph-01) in middle-aged and elderly Japanese population who participated in annual health check-ups (n = 784, 46–90 years old) (Abe et al., 2016).

2.4. Pulmonary function tests

After Zrs measurements, spirometry was performed and lung volumes were determined using computerized equipment (Fudak77, Fukuda Sangyo, Tokyo, Japan). The following spirometric parameters, vital capacity (VC), forced vital capacity (FVC), FEV_1, and forced expiratory flow from 25% to 75% of FVC ($FEF_{25\text{-}75}$), were assessed. Lung volumes including residual volume (RV) and total lung capacity (TLC) were measured by means of the helium dilution technique. Diffusion capacity of the lung for carbon monoxide (DL_{CO}) and its value corrected for alveolar volume (DL_{CO}/V_A) were measured by the single-breath technique. Data were given as % of the predicted values for spirometry and lung volumes calculated according to the method of the Japanese Respiratory Society. Data are also calculated as the % of predicted values according to the method of the Japanese Respiratory Society (Japanese-Respiratory-Society, 2004).

2.5. Interpretation of CT examinations

CT data were obtained using a 64- or 16-row multi-detector CT (Aquilion64 or Aquilion16; Toshiba Medical Systems Corp., Tokyo). Patients were scanned in the craniocaudal direction with inspiratory apnea. The slice thickness and reconstruction interval of high-resolution CT were 0.5-/1.0-mm and 0.5-/1.0-mm, respectively, using a high-spatial frequency algorithm. The radiological diagnosis was made by an experienced thoracic radiologist (S. Iwano) and defined based on a previous report by Tanaka et al. (Tanaka et al., 2004). He was blinded to the patients' clinical information except that all patients had RA. Then, the diagnosis was reviewed by chest physicians (Y.I. and M.T.). CT findings of IP features (airspace consolidation, ground glass opacity, reticulation, nodular opacity, and honeycombing) and airway abnormalities (bronchiectasis, bronchiolectasis, and bronchiolar abnormality) were assessed (Tanaka et al., 2004; Sokai et al., 2016) (supplementary Table 1). The extent of CT findings was graded subjectively with a five-point scale within the whole lung field as follows: grade 0, the finding was absent; grade 1, the percentage of involvement of the lungs was between 1% and 25%; grade 2, the percentage of involvement was between 26% and 50%; grade 3, the percentage of involvement was between 51% and 75%; and grade 4, the percentage of involvement was more than 76% (Tanaka et al., 2004). Each of the following CT findings, traction bronchiectasis, crazy-paving appearance, tree-in-bud sign, architectural distortion, pulmonary artery enlargement, esophageal dilatation, lymph node enlargement, pleural or pericardial effusion or thickening, and bronchiolar abnormality, was coded separately as present or absent (Sokai et al., 2016). RA-related IPs involve various histopathological types such as usual interstitial pneumonia, nonspecific interstitial pneumonia, diffuse alveolar damage, and organizing pneumonia (Yousem et al., 1985; Tanaka et al., 2004; Tsuchiya et al., 2011; Nakamura et al., 2012). However, a multiplicity of CT and histological patterns is commonly seen and different IP patterns or airway abnormalities can overlap in a patient with RA-related pulmonary diseases (Tanaka et al., 2004; Tsuchiya et al., 2011; Nakamura et al., 2012). Therefore, each CT finding was simply categorized as one of four types: airway lesion dominant, IP dominant, mixed (both airway lesion and IP), or others according to previous studies (Mori et al., 2012; Sokai et al., 2016; Matsumoto et al., 2018).

2.6. Adverse respiratory events

Adverse respiratory events including admission to the hospital, additional use of antibiotics or systemic corticosteroids, emergency room visits due to respiratory complications such as acute respiratory

Table 1
Patient characteristics and laboratory findings.

Variable	Total, n = 42	Airway, n = 17	IP, n = 13	P value
Age, year (range)	65.2 ± 8.0 (44-84)	65.2 ± 7.7	62.0 ± 7.1	0.294
Female, n (%)	N = 26 (61.9%)	N = 13 (76.5%)	N = 6 (46.2%)	0.132
Height, cm	156.9 ± 10.1	156.2 ± 8.5	160.0 ± 10.7	0.379
Body mass index	23.3 ± 5.3	22.3 ± 6.4	24.2 ± 3.9	0.023*
Duration of RA, year	11.6 ± 9.7	13.3 ± 9.6	10.0 ± 7.2	0.544
Smoker ever	N = 23 (54.8%)	N = 7 (41.2%)	N = 10 (76.9%)	0.054
Methotrexate ever	N = 25 (59.5%)	N = 14 (82.4%)	N = 4 (30.8%)	0.005*
Biologic agent ever	N = 23 (54.8%)	N = 9 (52.9%)	N = 7 (53.8%)	0.961
Chest CT pattern (Airway lesion/IP/mixed/others)	N = 17/13/4/8			
Pulmonary function test and FOT follow-up, day	1552 ± 399	1575 ± 414	1490 ± 416	0.645
Anti-CCP Ab, U/mL	171.5 ± 242.6, n = 32	171.3 ± 357.0, n=12	144.4 ± 130.6, n=8	0.320
RF, IU/mL	200.6 ± 346.6, n=31	120.1 ± 90.9, n=11	214.4 ± 228.9, n = 10	0.481
KL-6, U/mL	530.0 ± 382.4, n=36	395.6 ± 326.9, n = 13	739.0 ± 436.2, n=12	0.001*

Data are given as mean ± SD (range) or number (%).
* Significantly different (P < 0.05) between the airway lesion dominant (airway) and interstitial pneumonia dominant (IP) groups. Anti-CCP Ab, anti-cyclic citrullinated peptide antibody; RA, rheumatoid arthritis; RF, rheumatoid factor; SP-D, surfactant protein-D; FOT, forced oscillation technique; KL-6, Krebs von den Lungen-6.

infections, exacerbation of wheezing, exacerbation of interstitial pneumonia, and drug-induced lung injury were assessed.

2.7. Statistical analysis

Repeated-measure analysis of variance (ANOVA) followed by Tukey's *post hoc* test or a *t*-test was used to evaluate the statistical significance (SigmaPlot14.0; Systat Software Inc., San Jose, CA, USA). When data failed a normality test, ANOVA on ranks followed by Tukey's test or the Mann-Whitney test was used. P < 0.05 was considered statistically significant. Correlations between variables were analyzed using Spearman's rank or Pearson's correlation coefficient. Fisher's exact test or chi-square test was used to evaluate significance of group differences in various categories. Data are given as mean ± SD.

3. Results

3.1. Clinical characteristics

The baseline characteristics of 42 RA patients are shown in Table 1. Subjects were predominantly female (n = 26, 61.9%), and biologic agents were used in 23 cases (54.8%). Almost all (96.9%) were positive for anti-cyclic citrullinated peptide (anti-CCP) antibody, and 93.5% were positive for rheumatoid factor (RF). Chest CT patterns were airway lesion dominant in 17 cases (40.5%), and IP dominant in 13 cases (31.0%). The baseline characteristics of the airway lesion-dominant and IP-dominant groups are also compared in Table 1. Grades and frequencies of CT findings of the airway lesion-dominant and IP-dominant groups are compared in supplementary Table 1.

3.2. Long-term change in Zrs

Next, long-term changes in Zrs parameters were examined. The values of the first (baseline) and last assessment (follow-up intervals, 924–2209 days) were compared. The Rrs and Xrs results during a whole breath at a given frequency are shown in Fig. 1. The Rrs of the last assessment was significantly lower than that of the baseline at all frequencies (P < 0.05) (Fig. 1A). There was no significant difference in the Xrs between the groups (Fig. 1B). Rrs and Xrs of both baseline and last assessment were significantly frequency-dependent (P < 0.001) (Fig. 1A and B). Differences between inspiratory and expiratory phases in Zrs, $Rrs_{Insp\text{-}Exp}$ and $Xrs_{Insp\text{-}Exp}$, obtained from within-breath analysis of Zrs are also shown. There was no significant difference in $Rrs_{Insp\text{-}Exp}$ between the groups (Fig. 1C). The $Xrs_{Insp\text{-}Exp}$ of the last assessment was significantly lower than that of the baseline (Fig. 1D).

Rrs values at 20 Hz (R20) during a whole-breath, inspiration, and expiration of RA patients and those of the reference Japanese population (Abe et al., 2016) are shown in Table 2. The ages of RA patients at the baseline (44–84 years old) were similar to those of the reference ages (46–90 years old). In our RA cohort, R20 values during a whole-breath, inspiration, and expiration distributed higher than those in the reference population both in men and women.

3.3. Longitudinal changes in pulmonary function test parameters

Pulmonary function test results of the baseline and last assessment are compared in Table 3. Absolute values of VC, FVC, FEV_1, TLC, and DL_{CO} of the last assessment were significantly lower than those of the baseline (Table 3). In contrast, there was no significant difference in % of predictive values of the lung volume parameters except TLC (%TLC) (Table 3). Percentages of predicted values of DL_{CO} ($\%DL_{CO}$) and DL_{CO}/V_A ($\%DL_{CO}/V_A$) at the last assessment were significantly lower than the baseline values.

3.4. Correlations between annual changes in Zrs and pulmonary functions

Next, correlations between annual changes in parameters of the Zrs and pulmonary function test were examined. Rrs and Xrs values during a whole breath obtained at the lowest frequency (4 Hz) (R4 and X4), Rrs during a whole breath at 20 Hz (R20), and within breath analysis of Xrs at 4 Hz ($X4_{Insp\text{-}Exp}$) were selected for analysis. The annual change in X4 significantly correlated with that in VC (Table 4). The annual change in $X4_{Insp\text{-}Exp}$ significantly correlated with that in $FEF_{25\text{-}75}$. Relationships between annual changes in X4 and VC or $FEF_{25\text{-}75}$ are also shown in Fig. 2.

3.5. Comparisons of annual changes in pulmonary functions and Zrs between airway lesion-dominant and interstitial pneumonia-dominant groups

We compared the annual changes in pulmonary function tests and Zrs results of the airway lesion-dominant (n = 17) and IP-dominant (n = 13) groups. There was no significant difference in annual changes in pulmonary function parameters (Table 5), Rrs or Xrs (Fig. 3), between the groups.

3.6. Effects of adverse respiratory events on annual changes in Zrs

Results of adverse respiratory events that occurred between the first and last assessments of Zrs are shown in supplementary Table 2. A total

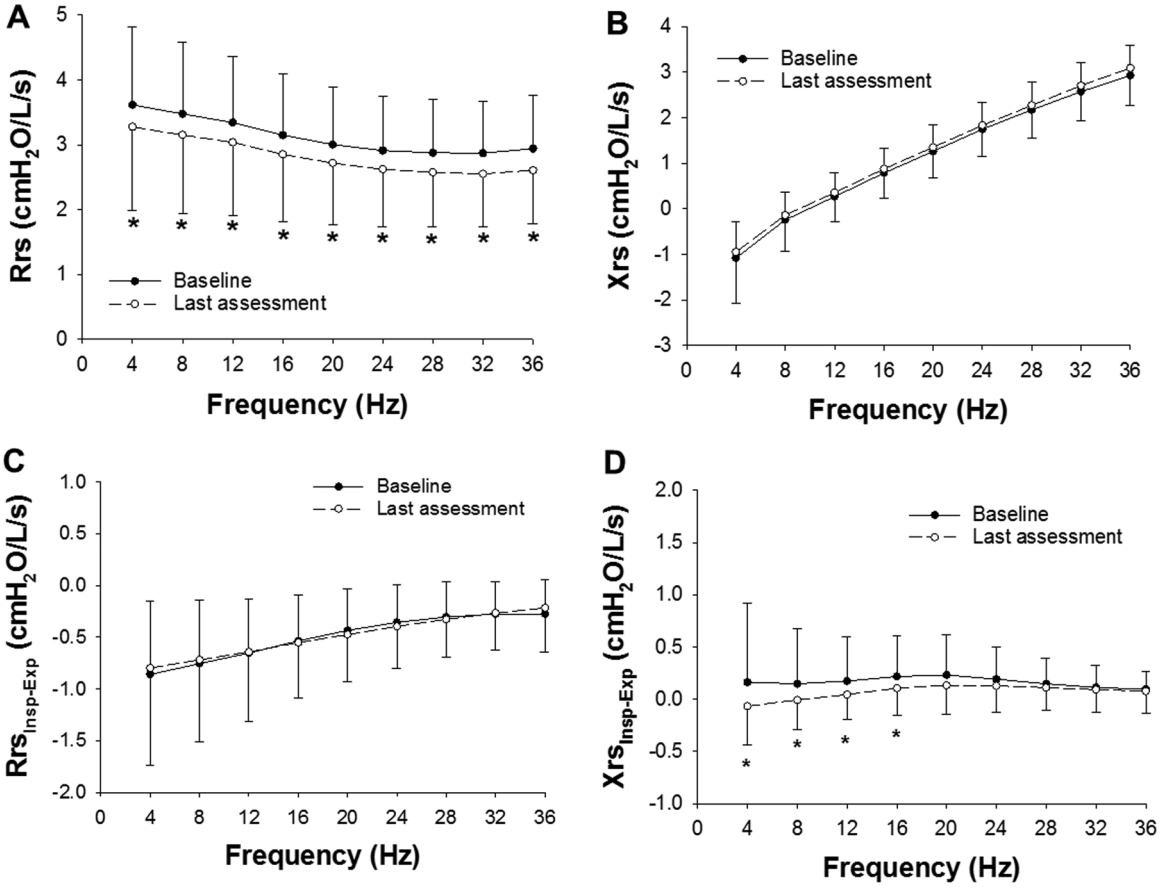

Fig. 1. Respiratory resistance (Rrs) and reactance (Xrs) at 4–36 Hz are shown. Rrs **(A)** and Xrs **(B)** during a whole breath at the baseline and the last assessment are compared. Differences between inspiratory and expiratory phases in Rrs ($Rrs_{Insp\text{-}Exp}$) **(C)** and Xrs ($Xrs_{Insp\text{-}Exp}$) **(D)** calculated as mean inspiratory values minus mean expiratory values at the baseline and the last assessment are compared. Follow-up intervals were 924–2209 days. Values are means ± SD (n = 42). *Significant difference ($P < 0.05$) between the values of the baseline and last assessment by two-way repeated measure ANOVA, followed by Tukey's test for post hoc analysis.

Table 2
Actual and reference values of Rrs at 20 Hz.

Variable	Baseline of RA, median [interquartile range] (range)	Last assessment of RA, median [interquartile range] (range)	Reference*, median [interquartile range]	Reference*, mean/1-SD from mean/ 2-SD from mean
Man	N = 16	N = 16	N = 368	N = 368
R20, whole	2.56 [1.78-3.07] (1.47-5.84)	2.20 [1.62-2.67] (1.13-5.38)	1.79 [1.48-2.26]	1.82/2.49/3.41
R20, expiration	2.72 [1.81-3.47] (1.58-5.86)	2.53 [1.68-3.00] (1.15-5.42)	1.86 [1.52-2.31]	1.88/2.58/3.56
R20, inspiration	2.34 [1.80-2.91] (1.34-5.82)	1.91 [1.54-2.59] (1.10-5.36)	1.72 [1.40-2.19]	1.75/2.44/3.39
Woman	N = 26	N = 26	N = 416	N = 416
R20, whole	3.09 [2.79-3.45] (1.57-4.53)	2.62 [2.26-3.33] (1.92-4.50)	2.36 [1.94-2.85]	2.36/3.25/4.46
R20, expiration	3.41 [3.04-3.78] (1.57-4.52)	2.92 [2.55-3.59] (1.91-4.78)	2.48 [2.03-3.01]	2.48/3.48/4.86
R20, inspiration	2.93 [2.49-3.29] (1.57-4.53)	2.36 [1.98-3.07] (1.56-4.37)	2.21 [1.82-2.71]	2.23/3.07/4.22

Ages of RA subjects at the baseline were 53–77 years old in man and 44–84 years old in woman. Ages of reference subjects were 46–89 years old in man and 47–90 years old in woman.

* Reference values were obtained from Abe, Y., et al., 2016. Respir Invest. 54, 148-155. Mean, 1-SD, and 2-SD of reference values were achieved by transforming the parameters into natural log values. RA, rheumatoid arthritis; SD, standard deviation; R20, whole, Rrs at 20 Hz during a whole breath; R20, expiration, Rrs at 20 Hz during an expiration; R20, inspiration, Rrs at 20 Hz during an inspiration.

of 58 adverse respiratory events occurred in 27 patients (64.3%). Patients were divided into two groups based on the frequency of respiratory adverse events per year. The high frequency group (n = 10) was defined as a rank in the top quartile of the incidence of respiratory adverse events. The clinical characteristics, annual changes in parameters of pulmonary function tests, and the Zrs results of the high frequency (n = 10) and low frequency respiratory event groups (n = 32) are compared in supplementary Table 3 and supplementary Figs. 2 and 3. The Rrs of the high frequency group at the baseline was significantly higher than that of the low frequency group (supplementary Fig. 2A). Annual changes in Xrs were significantly different at 4 and 36 Hz between the groups (supplementary Fig. 3B).

4. Discussion

The main findings of the present study were that in patients with RA: 1) Rrs at all frequencies and $X_{Insp\text{-}Exp}$ at 4–16 Hz were significantly decreased during a > 900-day (924 to 2209-day) interval, 2) the % of predictive values of TLC, DL_{CO}, and DL_{CO}/V_A significantly decreased during the > 900-day interval, 3) annual changes in Xrs parameters significantly correlated with those of VC and $FEF_{25\text{-}75}$, 4) annual changes in Zrs or pulmonary function test results were not significantly

Table 3
Longitudinal and annual changes in pulmonary function test parameters.

Variable	Baseline	Last assessment	P value	Change, /year
VC, L	2.85 ± 0.70	2.76 ± 0.75	0.004*	−0.025 ± 0.061
%VC	97.3 ± 14.8	97.5 ± 15.8	0.906	
FVC, L	2.79 ± 0.68	2.68 ± 0.74	0.005*	−0.026 ± 0.066
%FVC	99.8 ± 16.7	99.8 ± 17.7	0.995	
FEV_1, L	2.00 ± 0.55	1.91 ± 0.56	0.001*	−0.024 ± 0.046
$\%FEV_1$	88.2 ± 18.3	89.1 ± 19.5	0.462	
FEV_1/FVC, %	71.5 ± 9.0	71.3 ± 10.4	0.767	−0.01 ± 1.37
FEF_{25-75}	1.46 ± 0.73	1.34 ± 0.71	0.077	−0.024 ± 0.106
$\%FEF_{25-75}$	52.8 ± 25.1	53.0 ± 27.0	0.938	
TLC, L (n = 37)	4.57 ± 0.92	4.45 ± 0.97	0.018*	−0.040 ± 0.110
%TLC (n = 37)	103.0 ± 13.0	99.4 ± 14.1	0.017*	
RV, L (n = 37)	1.69 ± 0.42	1.68 ± 0.43	0.394	−0.012 ± 0.080
%RV (n = 37)	100.5 ± 22.9	96.4 ± 23.4	0.062	
RV/TLC, % (n = 37)	37.3 ± 7.1	38.2 ± 7.8	0.383	0.135 ± 1.115
DLco, mL/min/mmHg (n = 37)	16.5 ± 4.5	14.8 ± 4.1	< 0.001*	−0.402 ± 0.625
%DLco (n = 37)	97.1 ± 24.1	90.5 ± 21.6	< 0.001*	
$\%DLco/V_A$ (n = 37)	101.4 ± 29.1	97.1 ± 25.8	0.035*	

N = 42 otherwise indicated. *Significantly different (P < 0.05).

Table 4
Correlation between annual changes in pulmonary function test and Zrs parameters.

		VC	FVC	FEV_1	FEV_1/FVC	FEF_{25-75}	DL_{CO}, n = 37
R4	Rho	−0.008	0.024	−0.033	−0.085	−0.204	−0.039
	P	0.958	0.880	0.835	0.594	0.195	0.821
R20	Rho	0.125	0.112	0.065	−0.130	−0.192	0.037
	P	0.430	0.478	0.683	0.410	0.223	0.829
X4	Rho	0.306	0.118	0.264	−0.037	0.233	0.228
	P	0.049*	0.455	0.092	0.814	0.138	0.176
$X4_{Insp-Exp}$	Rho	−0.172	0.115	−0.162	−0.141	−0.381	−0.161
	P	0.275	0.468	0.305	0.372	0.013*	0.342

Values (rho) are Spearman's rank correlation coefficients. *Significant correlation (P < 0.05). N = 42 otherwise indicated.

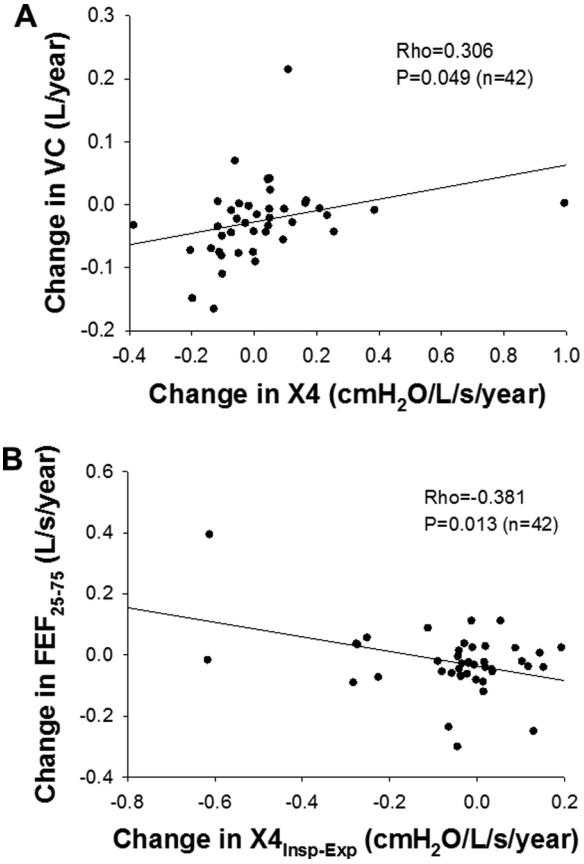

Fig. 2. Significant correlations between annual changes in pulmonary function tests and Xrs parameters. A correlation between the annual change in Xrs at 4 Hz during a whole breath (X4) and the annual change in vital capacity (VC) **(A)** and a correlation between the annual change in $Xrs_{Insp-Exp}$ and annual change in forced expiratory flow from 25% to 75% of forced vital capacity (FEF_{25-75}) **(B)** are shown (n = 42).

different between the airway lesion dominant and IP dominant groups, and 5) Zrs parameters, Rrs at 4, 8, 12, and 36 Hz, Xrs at 4 Hz, and annual changes in Xrs at 4 and 36 Hz, were significantly different between the low and high frequency respiratory adverse event groups. To our knowledge, this is the first study to characterize the long-term changes in Zrs measured by FOT and to relate the Zrs results to pulmonary functions and CT findings in patients with RA-related pulmonary diseases.

In the analysis of spirometric volume parameters of all cases, the absolute values of VC, FVC, and FEV_1, were significantly decreased during a > 900-day interval, but the % of predicted values of these parameters was not (Table 3). In contrast, both the absolute and % of predicted values of TLC and DL_{CO} of the last assessment were significantly lower than those at the baseline (Table 3). Declines of some pulmonary function parameters over long intervals in RA have been reported (Linstow et al., 1994; Beyeler et al., 1996; Zamora-Legoff et al., 2017). Our results are consistent with findings of these previous reports. It is likely that pulmonary functions remained in a relatively stable condition during observation periods in our RA patients who were able to undergo the follow-up pulmonary function test and Zrs measurement. Similar findings were reported for a non-smoking RA cohort (Fuld et al., 2003).

The Rrs of the last assessment was significantly lower than that at the baseline at all frequencies between 4 and 36 Hz (Fig. 1A). Because the Rrs reflects the extent of airflow obstruction, it is expected that a decrease in the Rrs correlates with an increase in spirometric parameters such as FEV_1 in both long- and short-term investigations in asthma and COPD (Ito et al., 2017; Kamada et al., 2017a,b). Effects of the type of respiratory disease and complications of respiratory adverse events on the changes in the Rrs were examined, but the changes in Rrs between the baseline and last assessment were not different between the airway lesion- and IP-dominant groups (Fig. 3A) or between the low and high frequency adverse respiratory event groups (supplementary Fig. 3A). Although the origin of this discrepancy between the long-term changes in Rrs and spirometric parameters is unclear, characteristics of respiratory mechanics in RA-related pulmonary diseases may be

Table 5
Comparison of changes in pulmonary function data between airway lesion-dominant and interstitial pneumonia-dominant groups.

Change	Airway, n = 17	IP, n = 13	P value
VC, L/year	−0.0408 ± 0.0440	0.0051 ± 0.0760	0.066
FVC, L/year	−0.0396 ± 0.0441	−0.0032 ± 0.0817	0.241
FEV_1, L/year	−0.0339 ± 0.0432	−0.0123 ± 0.0556	0.239
FEF_{25-75}, L/year	−0.038 ± 0.084	−0.055 ± 0.946	0.867
TLC, L/year	−0.0626 ± 0.118, n = 14	−0.00228 ± 0.126	0.211
DLco, mL/min/mmHg/year	−0.466 ± 0.529, n = 14	−0.116 ± 0.763	0.175

Values are mean ± SD.

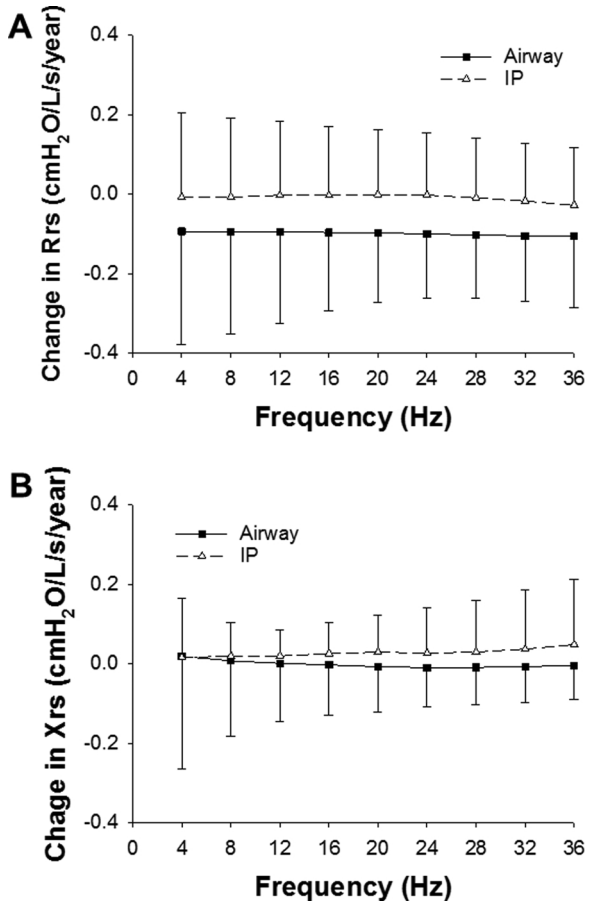

Fig. 3. Annual changes in Rrs **(A)** and Xrs **(B)** at 4–36 Hz during a whole breath of the airway lesion-dominant (airway) (n = 17) and interstitial pneumonia (IP)-dominant (n = 13) groups are compared. Differences between inspiratory and expiratory phases in Rrs ($Rrs_{Insp-Exp}$) **(C)** and Xrs ($Xrs_{Insp-Exp}$) **(D)** of the airway lesion-dominant and IP-dominant groups are also compared. Values are means ± SD.

different from those of obstructive airway diseases such as asthma and COPD. Our findings further support the idea that FOT is not a surrogate test for spirometry but should be used concomitantly (Akita et al., 2017).

We examined the Zrs data at a given frequency and found that the significant frequency dependence of the Rrs in RA was not different between the baseline and last assessment (Fig. 1). The frequency dependence of Rrs reflects the inhomogeneity of gas flow in the respiratory system, specifically during bronchoconstriction (van Noord et al., 1989; Pride, 1992; Lutchen et al., 1996). We previously demonstrated that Rrs depends on the frequency between 4 and 36 Hz in RA-related pulmonary diseases but not in healthy subjects (Sokai et al., 2016). Thus, our results suggest that the airflow inhomogeneity existed and did not change during > 900-day interval in our RA cohort. In order to evaluate the airflow inhomogeneity in RA-related pulmonary diseases, other respiratory function assessments such as a single breath N_2 washout, closing volume, and lung clearance index would be beneficial as used in asthma and COPD (Shirai et al., 2013).

The Xrs values were not different between the baseline and last assessment (Fig. 1B), but the annual change in X4 during a whole breath significantly correlated with that in VC (Fig. 2A). It is generally known that Zrs values are affected by lung volume (van den Elshout et al., 1990; Hirai et al., 1999; Ito et al., 2007). Thus, it is considered that the change in lung volume affected the X4 values during a follow-up period in our RA patients. Zrs parameters, specifically Xrs at low frequency, are more sensitive than FEV_1 for detection of a change in bronchial tone in asthma and COPD in the clinical setting (Kolsum et al., 2009; Akita et al., 2017; Ito et al., 2017). Kolsum et al. examined the relationship between the Zrs and spirometric results in a one-year follow-up study of COPD patients and found that changes in Xrs at 5 Hz correlated with % changes in FEV_1, but those in Rrs at 5 Hz did not (Kolsum et al., 2009). More recently, Akita et al. found a significant correlation between changes in FEV_1 and Xrs parameters in a five-year follow-up study of COPD (Akita et al., 2017). These results indicate that Xrs measurements are also useful to evaluate year-to-year or long-term changes in the respiratory mechanics of the same individual with COPD as well as RA.

The within-breath behavior of the Zrs results showed that $Rrs_{Insp-Exp}$ was not changed, but that $Xrs_{Insp-Exp}$ was significantly decreased during a > 900-day interval (Fig. 1). The changes in $X4_{Insp-Exp}$ and FEF_{25-75} show a significant negative correlation (Fig. 2B). It has been reported that Rrs is higher during the expiratory phase, but Xrs is not different between the expiratory and inspiratory phases in healthy subjects (Kanda et al., 2010; Sokai et al., 2016). Dellaca et al. analyzed individual respiratory cycles and reported that a large difference in Xrs between inspiratory and expiratory phases at low frequencies is useful for detecting an expiratory flow limitation in patients with COPD (Dellaca et al., 2004). Therefore, $Xrs_{Insp-Exp}$ at low frequencies, specifically 5 Hz, has been used as an indicator of expiratory flow limitation (Mori et al., 2013; Ito et al., 2017; Kamada et al., 2017a,b). Moreover, previous studies have demonstrated that the inspiratory Xrs of IP at a low frequency is significantly lower than the expiratory Xrs different from the findings in COPD (Mori et al., 2013; Sugiyama et al., 2013; Shirai and Kurosawa, 2016).

The Rrs at 4, 8, 12, and 36 Hz and X4 of the baseline were significantly different between the groups with low and high frequency of adverse respiratory events (supplementary Fig. 2). In contrast, there was no significant difference in pulmonary function test parameters between the groups (supplementary Table 3). Matsumoto et al. recently reported that the incidence of respiratory adverse events in RA patients with pre-existing respiratory involvement specifically IP and airway abnormalities based on CT findings is higher than that without respiratory involvement during biological DMARDs therapy (Matsumoto et al., 2018). FOT may be a useful tool to predict future risks for pulmonary complications in RA-related pulmonary disease. However, due to our small sample size, identifying the risk factors for respiratory adverse events is beyond the scope of the present study. Further studies will be important.

This study has several limitations. The data were retrospectively collected from RA patients with respiratory diseases or pulmonary involvement without data from RA subjects who do not have pulmonary involvement. Because heterogeneity is one of characteristics of RA-related pulmonary abnormalities, it may be difficult to determine features of the respiratory mechanics of RA. Another issue is that the baseline pulmonary function test results in the most of the present patients were normal (Table 3). Prospective studies with a larger number of subjects including control RA subjects and subjects with different pulmonary diseases with different severities and various IP subtypes are necessary

to characterize the Zrs of RA. Moreover, the Zrs data vary between different FOT devices used for the measurements and normative reference values have not been established (Oostveen et al., 2013; Shirai and Kurosawa, 2016; Kalchiem-Dekel and Hines, 2018). Although it is considered that the Zrs values of young subjects and elderly ones would be different, associations between age and Zrs parameters specifically Rrs are generally inconsistent (Shiota et al., 2005; Kalchiem-Dekel and Hines, 2018). In our cohort, it is unlikely that Zrs data are largely affected by aging during < 6.1-year interval. Future studies are necessary to establish the methodology, reference values, and effects of aging for Zrs measurements.

In summary, long-term changes in respiratory mechanics together with pulmonary functions were characterized in patients with RA-related pulmonary diseases. A significant decrease during a > 900-day interval with frequency-dependent behavior was found in the Rrs. The annual changes in Xrs parameters were correlated with those in spirometric parameters. FOT combined with spirometry may be beneficial to evaluate alterations in respiratory functions in RA patients.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2018.12.008.

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